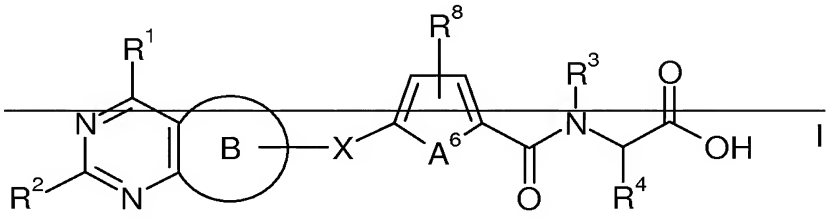
AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method of combating toxicity caused by raltitrexed ~~an antifolate compound of Formula I,~~

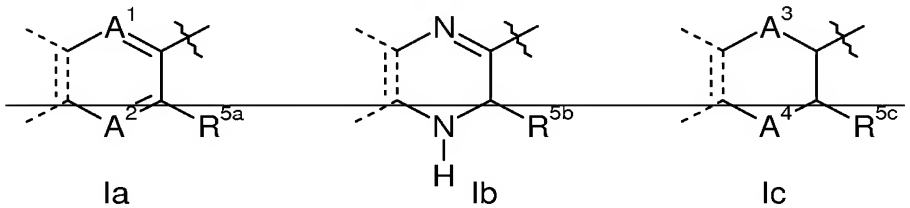


~~wherein~~

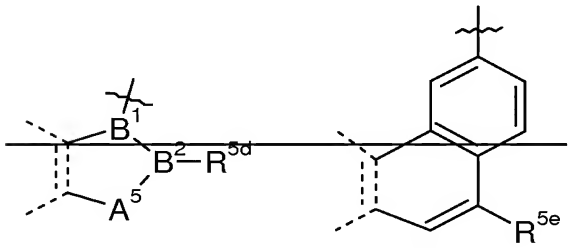
~~R^1 represents NH_2, OH or CH_3;~~

~~R^2 represents NH_2 or C_{1-4} alkyl;~~

~~the group B represents a structural fragment of Formula Ia, Ib, Ic, Id or Ie,~~



Ia Ib Ic



Id Ie

~~in which groups the dashed lines indicate the point of ring fusion with the pyrimidinyl ring and the wavy lines indicate the point of attachment of the structural fragments to the group X;~~

~~R^{5a} to R^{5e} independently represent H or C_{1-4} alkyl;~~

~~A^1 represents $C(R^{6a})$ or N;~~

~~A^2 represents CH or N;~~

~~A^3 represents $C(H)R^{6b}$, NR^{6e} or S;~~

~~A^4 and A^5 independently represent CH_2, NH, O or S;~~

~~the group B^1-B^2 represents CH-CH or C=C;~~

~~R^{6a} to R^{6e} independently represent H or C_{1-4} alkyl, or R^{6e} represents $C(O)R^{6d}$, or R^{6e}, together~~

~~with R^{7b} represents C_{1-2} *n* alkylene;~~

~~R^{6d} represents H or C_{1-4} alkyl;~~

~~X represents $CH_2C(H)R^{7a}$ or CH_2NR^{7b} (in which latter two groups the CH_2 moiety is attached to the fused, pyrimidine-based heterocyclic group);~~

~~R^{7a} and R^{7b} independently represent H, C_{1-6} alkyl, C_{3-6} alkenyl or C_{3-6} alkynyl, or R^{7b}, together with R^{6e} represents C_{1-2} *n* alkylene;~~

~~A^6 represents O or S;~~

~~R^8 represents H or one or two substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy;~~

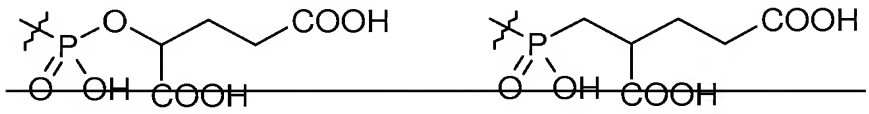
~~R^3 represents H or C_{1-4} alkyl;~~

~~R^4 represents $CH_2C(R^{9a})(R^{9b})$ D;~~

~~R^{9a} and R^{9b} independently represent H or C_{1-4} alkyl, or R^{9a} and R^{9b} together represent $=C(H)R^{10}$;~~

~~R^{10} represents H or C_{1-4} alkyl;~~

~~D represents C(O)OH, tetrazol-5-yl, $(CH_2)_{0-1}NHR^{11}$, or, when R^{9a} and R^{9b} together represent $=C(H)R^{10}$, then D may also represent H, or D represents a structural fragment of Formula IIIa or IIIb,~~



IIIa IIIb

~~wherein the wavy lines indicate the point of attachment of the structural fragments;~~

~~R^{11} represents H or $C(O)R^{12}$;~~

~~R^{12} represents H or phenyl substituted by C(O)OH and optionally substituted by one or two further substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy; and~~

~~alkyl, alkenyl and alkynyl groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms;~~

or a pharmaceutically acceptable salt and/or solvate thereof,

in an individual ~~who has been administered said compound~~, the method comprising administering ~~to the individual an enzyme that has carboxypeptidase G activity~~ carboxypeptidase G_2 (EC 3.4.22.12) to the individual.

2. (Canceled)

3. (Currently amended) A method according to Claim 1 ~~or 2~~ wherein the individual is administered the carboxypeptidase G_2 ~~the enzyme that has carboxypeptidase G activity~~ between about 24 and 48 hours after being administered the raltitrexed or salt or solvate thereof ~~antifolate compound~~.

4. (Currently amended) A method according to Claim 1 ~~any of Claims 1 to 3~~ wherein the individual has one of more clinical markers of toxicity caused by raltitrexed ~~the antifolate compound~~.

5. (Currently amended) A method according to Claim 4 wherein the clinical marker of toxicity caused by raltitrexed ~~the antifolate compound~~ is a plasma level of raltitrexed ~~the compound~~ greater than a ~~predetermined~~ plasma level indicating toxicity at a given time after administration ~~of the compound~~.

6. (Currently amended) A method according to Claim 5 wherein the ~~predetermined blood~~ plasma level of raltitrexed ~~the antifolate compound~~ indicating toxicity is 1μM at 24 hours after administration ~~of the compound~~.

7. (Currently amended) A method according to Claim 5 ~~or 6~~ further comprising the prior step of determining the plasma level of raltitrexed ~~the antifolate compound~~ in the individual at a given time after administration ~~of the compound~~.

8. (Currently amended) A method according to Claim 1 ~~any of Claims 1 to 7~~ wherein the individual has one or more clinical symptoms of toxicity caused by raltitrexed ~~the antifolate compound~~.

9. (Currently amended) A method according to Claim 8 wherein the one or more clinical symptom of toxicity caused by raltitrexed ~~the antifolate compound is~~ are selected from the group consisting of anaemia, anorexia, asthenia, dehydration, diarrhoea, ~~fatigue, fever,~~ hepatotoxicity, ~~hyperbilirubinaemia, leukopaenia,~~ mucositis, myelosuppression, nausea, and neutropaenia~~, rash, reversible transaminitis, stomatitis, thrombocytopaenia and vomiting~~.

10. (Currently amended) A method according to Claim 8 ~~or 9~~ further comprising the prior step of determining the presence of the one or more clinical symptoms of toxicity caused by raltitrexed ~~the antifolate compound~~ in the individual.

11. (Currently amended) A method according to Claim 1 ~~any of Claims 1 to 10~~ and further comprising administering a folate pathway rescue agent to the individual.

12. – 13. (Canceled)

14. (Currently amended) A method according to Claim 11 wherein the ~~antifolate compound of Formula I is an inhibitor of thymidylate synthase (TS), and~~ the folate pathway rescue agent is thymidine.

15. (Canceled)

16. (Currently amended) A method according to Claim 11 ~~any of Claims 11 to 15~~ wherein the individual is administered the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~ prior to the folate pathway rescue agent.

17. (Currently amended) A method according to Claim 11 ~~any of Claims 11 to 15~~ wherein the individual is administered the folate pathway rescue agent prior to the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~.

18. (Currently amended) A method according to Claim 11 ~~any of Claims 11 to 15~~ wherein the individual is administered the folate pathway rescue agent and the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~ substantially simultaneously.

19. (Currently amended) A method according to Claim 1 ~~any of Claims 1 to 18~~ wherein the individual is administered the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~ at a dose of about 50 Units per kg body weight.

20. – 49. (Canceled)

50. (Currently amended) A method of monitoring the effectiveness of carboxypeptidase G_2 (EC 3.422.12) in combating raltitrexed toxicity in an individual *in vivo* ~~determining the rate and/or extent of cleavage of a compound of Formula I as defined in Claim 1 or Claim 2 by an enzyme that has carboxypeptidase G activity~~, the method comprising:

providing an individual who has been administered raltitrexed ~~the compound of Formula I~~,

contacting the raltitrexed ~~compound of Formula I~~ with the carboxypeptidase G_2 ~~an enzyme that has carboxypeptidase G activity~~ under conditions such that cleavage of them raltitrexed ~~compound~~ can occur, and

monitoring the rate and/or extent of cleavage of the raltitrexed ~~compound of Formula I~~ over time.

51. (Currently amended) A method according to Claim 50 wherein the monitoring step comprises monitoring the amount, concentration, or both ~~and/or concentration~~ of the raltitrexed ~~compound of Formula I~~.

52. (Currently amended) A method according to Claim 50 ~~or 51~~ wherein the monitoring step comprises monitoring the amount, concentration, or both ~~and/or concentration~~ of one or more break-down products of raltitrexed ~~the compound of Formula I~~.

53. - 54. (Canceled)

55. (Currently amended) A method according to Claim 50 ~~Claim 54~~ further comprising determining whether an additional dose of the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~ is required in order reduce the amount of the raltitrexed ~~compound of Formula I~~ to a non-toxic ~~predetermined~~ level.

56. (Currently amended) A method according to Claim ~~54 or~~ 55 further comprising contacting the raltitrexed ~~compound of Formula I~~ with an additional dose of the carboxypeptidase G_2 ~~enzyme that has carboxypeptidase G activity~~ under conditions such that cleavage of the ~~compound~~ raltitrexed can occur.

57. – 63. (Canceled)

64. (New) A method of combating toxicity caused by raltitrexed which has been administered to a human individual for the treatment of cancer, the method comprising:

administering raltitrexed or a pharmaceutically acceptable salt and/or solvate thereof to the individual;

subsequently determining whether the individual has a clinical marker of raltitrexed toxicity and/or one or more clinical symptoms of raltitrexed toxicity; and

if the individual has a clinical marker of raltitrexed toxicity and/or one or more clinical symptoms of raltitrexed toxicity, administering to the individual carboxypeptidase G_2 (EC 3.4.22.12).

65. (New) A method according to Claim 64 wherein the clinical marker of raltitrexed toxicity is a plasma level of raltitrexed greater than a plasma level indicating toxicity at a given time after administration.

66. (New) A method according to Claim 65 wherein the plasma level of raltitrexed indicating toxicity is 1μM at 24 hours after administration.

67. (New) A method according to Claim 64 wherein the one or more clinical symptoms of raltitrexed toxicity are selected from the group consisting of anaemia, asthenia, dehydration, diarrhoea, hepatotoxicity, mucositis, myelosuppression, nausea and neutropaenia.

68. (New) A method according to Claim 64 further comprising administering thymidine to the individual.

69. (New) A method according to Claim 64 wherein the individual has a cancer selected from the group consisting of cancer of the breast, ovary, colon/rectum, liver, prostate, pancreas or stomach, or non small cell lung cancer, malignant mesothelioma and carcinoma of unknown primary.

70. (New) A method according to Claim 64 wherein the individual has colorectal cancer.